REMARKS

Applicants respectfully request entry of the present amendment and reconsideration of the claims currently pending. With entry of this amendment, claims 1-14 will be pending in the present application. Applicant has amended claims 1-11 and added new claims 12-14 to more particularly claim the present invention. Further, Applicant has amended the original claims to address the Examiner's rejection of these claims under 35 U.S.C. § 112. Applicant submits that the Examiner's rejections under Section 112 have been overcome and respectfully request that the Examiner withdraw these rejections.

In the Office Action, claims 1-10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Hoffmann, et al. (Clin. Chem. 35(4): 587-595 [4/1989]) in view of Galjaard (Ballieres Clin. Obst. Gyn. 1(3): 547-567 [9/1987]). Applicants submit that none of the cited references, either alone or in combination, disclose, teach, or otherwise suggest the claimed subject matter of all of the limitations of the currently pending claims as amended. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections.

As amended, the present claims are directed to methods for characterizing the levels of a plurality metabolites in an amniotic fluid sample relative to the levels of those metabolites in a control profile in order to treat an chromosomal abnormality in a fetus. A chromosome contains a plurality of genes controlling a plurality of enzymatic activities. Therefore, to treat a chromosomal abnormality, such as, e.g., Down Syndrome, the present claims are directed to methods of generating and analyzing a profile of a plurality of metabolites in a sample, and prescribing treatment for each metabolite with an abnormal level compared to a normal patient profile. The patient profile is used to identify particular metabolite deficiencies or surpluses, and treatment is prescribed based upon the metabolite deficiencies or surpluses. In particular,

Applicant has found that a global analysis of a plurality of metabolites, in contrast to examination and treatment of specific, individual metabolites and specific inborn errors of metabolism, results in more accurate diagnosis and treatment of chromosomal abnormalities, including Down Syndrome.

The cited references either alone or in combination fail to disclose, teach, or suggest the identification and treatment of a plurality of metabolites, via the generation and analysis of a patient profile containing data on a plurality of metabolites, in order to treat a chromosomal abnormality. For example, Hoffmann, et al. generally teaches a method for qualitative and quantitative determination of organic acids, aldehydes, and ketones in urine, plasma, or amniotic fluid samples that requires no deproteinization. Unlike the present claims, Hoffmann, et al. fails to teach or suggest the identification of increased or decreased levels of a plurality of metabolites during a single procedure, and relative to a control profile, and the prescribing of appropriate cofactors or blocking of the appropriate enzymes based on the identification of differing levels of the plurality of metabolites, in order to treat a chromosomal abnormality, such as Down Syndrome, in a fetus.

Galjaard, likewise, fails to disclose, teach, or suggest the limitations of the present claims that require the identification and treatment of a plurality of metabolites having differing levels compared to a control, during a single procedure to treat a chromosomal abnormality in a fetus. In contrast, Galjaard merely surveys a history of fetal diagnosis of inborn errors of metabolism. Galjaard states generally that, "the presence or absence of specific metabolites may be indicative of a particular genetic metabolic disease." (Galjaard at p. 549). Galjaard, however, fails to teach, disclose, or suggest the identifying of increased or decreased levels of a plurality of metabolites during a single procedure in order to identify and treat chromosomal abnormalities.

Galjaard merely teaches the identification and treatment of individual metabolic diseases, in contrast to the present claims which are directed at the identification and treatment of chromosomal disorders, i.e., disorders that are diagnosed and treated by analysis of a plurality of metabolites and a plurality of classes of metabolites, during a single procedure.

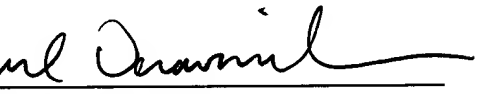
CONCLUSION

By entry of this Amendment, Applicant respectfully submits that all of the Examiner's rejections have been overcome. Applicant respectfully requests that the Examiner reconsider and withdraw the outstanding rejections and allow the present application. If, however, the Examiner still regards either of the Hoffmann, et al. or Galjaard references, either alone or in combination, to have some relevance to the present invention, Applicant respectfully requests that the Examiner provide a further, detailed explanation as to how and where the reference discloses each limitation of the present claims. Additionally, the Examiner is invited to telephone the undersigned representative if the Examiner believes that a telephonic interview would advance this case to allowance.

Respectfully submitted,

LYON & LYON LLP

Dated: April 4, 2001

By: 
Polaphat Veravanich
Reg. No. 45,179

PV/am
Lyon & Lyon LLP
633 West Fifth Street, Suite 4700
Los Angeles, California 90071-2066
(949) 567-2300

MARKED SET OF AMENDED CLAIMS

1. (Amended) A method of [characterizing] treating a chromosomal abnormality in a fetus by performing a comprehensive biochemical analysis of a plurality of metabolites in [of] a specimen of [amniotic] bodily fluid from a patient comprising:

obtaining a [comprehensive] patient profile of a plurality of metabolites contained in the specimen [of amniotic fluid] by measuring the level of each metabolite in the specimen,

[comparing the profile with a control profile of metabolites that is representative of normal levels of metabolites,]

generating a biochemical characterization of the chromosomal abnormality in the fetus, wherein the characterization comprises a list of each of the plurality of metabolites of the patient profile, measured during the obtaining step, with the level of each respective metabolite,

analyzing the plurality of metabolites of the patient profile with respect to [the normal] a control profile of the metabolites, the control profile being representative of normal levels of the metabolites, by identifying each metabolite [that has] having a different level [when compared] in comparison with the normal level of that metabolite, and

[generating a biochemical characterization of the abnormality,]

prescribing a biochemical treatment for each respective metabolite [that has] having a different level when compared with the normal level of that metabolite.

2. (Amended) The method of Claim 1 wherein [comparing] the analyzing the patient profile with [respect to] the [normal] control profile step is accomplished by comparing

the levels of metabolites in the patient profile with the mean levels and standard deviations for each respective metabolite of the control profile.

3. (Amended) The method of Claim 1 wherein [comparing] the analyzing the patient profile with [respect to] the [normal] control profile step is accomplished by [comparing median levels using a nonparametric analysis for each metabolite.] using a nonparametric analysis to compare the levels of metabolites in the patient profile with the median levels of each respective metabolite of the control profile.

4. (Amended) The method of Claim 1 wherein [Down Syndrome is the chromosomal abnormality that is diagnosed.] the analyzing step comprises:

determining if a formiminoglutamic acid level of the patient profile is less than a formiminoglutamic acid level of the control profile to analyze a level of mono-carbon in the patient profile relative to a level of mono-carbon in the control profile,

determining if a homocysteine level of the patient profile is increased relative to a homocysteine level of the control profile to analyze the level of homocysteine in the patient profile,

determining if a normetanephrine level of the patient profile is increased relative to a normetanephrine level of the control profile to analyze the level of normetanephrine in the patient profile,

determining if an oxalic acid level of the patient profile is decreased relative to an oxalic acid level of the control profile to analyze a level of vitamin B6 in the patient profile relative to a level of vitamin B6 in the control profile,

determining if a serine level of the patient profile is decreased relative to a serine level of the control profile to analyze the level of serine in the patient profile, and

determining if a tetra-hydro-biopterin level of the patient profile is decreased relative to a tetra-hydro-biopterin level of the control profile to analyze the level of tetra-hydro-biopterin in the patient profile.

5. (Amended) The method of Claim 1 wherein [the metabolite is chosen from the group consisting of organic acids, amino acids, neurotransmitters, fatty acids, glycine conjugates, drugs, drug metabolites, hormones, vitamins, and carbohydrates.] the prescribing comprises:

prescribing a mono-carbon related supplement to be ingested by the patient if the mono-carbon level in the patient profile is less than the mono-carbon level in the control profile, wherein the mono-carbon related supplement is a supplement chosen from the group consisting of folate, vitamin B12, and a mono-carbon donor,

prescribing a homocysteine related supplement to be ingested by the patient if the homocysteine level in the patient profile is increased relative to the homocysteine level in the control profile, wherein the homocysteine related supplement is a supplement chosen from the group consisting of folate, vitamin B6, vitamin B12, and a mono-carbon donor,

prescribing a normetanephrine related supplement to be ingested by the patient if the normetanephrine level in the patient profile is increased relative to the normetanephrine level in the control profile, wherein the normetanephrine related supplement is a supplement chosen from the group consisting of folate, vitamin B12, and a mono-carbon donor,

prescribing vitamin B6 to be ingested by the patient if the vitamin B6 level in the patient profile is decreased relative to the vitamin B6 level in the control profile,

prescribing serine to be ingested by the patient if the serine level in the patient profile is decreased relative to the serine level in the control profile, and

prescribing tetra-hydro-biopterin to be ingested by the patient if the tetra-hydro-biopterin level in the patient profile is decreased relative to the tetra-hydro-biopterin level in the control profile.

6. (Amended) The method of Claim 1 wherein the analyzing step is performed by analyzing multiple categories of metabolite groups [metabolites comprise multiple categories of metabolite groups that are analyzed] simultaneously.

7. (Amended) A method of performing a comprehensive biochemical analysis of a specimen of [amniotic] bodily fluid from a patient in order to [characterize a chromosomal abnormality] treat Down Syndrome in a fetus comprising:

obtaining a [comprehensive] patient profile of a plurality of metabolites present in the specimen of [amniotic] bodily fluid,

generating a global biochemical characterization of the abnormality in the fetus, wherein the global biochemical characterization comprises a list containing the name and level of each metabolite of the patient profile identified in the obtaining step,

[comparing the patient profile with a control profile of metabolites that is representative of normal levels of the reported metabolites,]

analyzing the metabolites contained in the patient profile with respect to [the normal] a control profile of metabolites, the control profile being representative of normal levels of the metabolites contained in the patient profile, by identifying each metabolite of the patient profile

that has a different level when compared with the [normal] level of that respective metabolite in the control profile, the analysis being performed for more than one metabolite,

[inferring]determining an activity level for an enzyme that corresponds to [the identified] each respective metabolite identified in the analyzing step, wherein the respective enzyme is an enzyme that metabolizes a substrate to form the respective metabolite, and

[inferring a cofactor level based on the activity level for the enzyme,]

[generating a global biochemical characterization of the abnormality,]

prescribing a biochemical treatment for each metabolite of the patient profile that has a different level when compared with the [normal] level[s] of that respective metabolite in the control profile, wherein the prescribing step comprises

prescribing a cofactor supplement if the enzyme activity for a metabolite of the patient profile is low relative to the level of that metabolite in the control profile, the cofactor being a cofactor that increases the activity of the respective enzyme.

8. (Amended) A method of characterizing the levels of a plurality of metabolites that are present in a fetus with a chromosomal abnormality [in a fetus] by performing a comprehensive biochemical analysis of a specimen of amniotic fluid from a patient comprising:

obtaining a [comprehensive] patient profile of a plurality of metabolites present in the specimen of amniotic fluid using a gas chromatograph/mass spectrometer system,

comparing the patient profile with an abnormal profile, wherein the abnormal profile represents a control profile of metabolite[s] levels that [is] are representative of levels of metabolites in patients suffering from [the chromosomal abnormality] Down Syndrome, and

analyzing the patient profile with respect to the [chromosomal] abnormal[ity] profile by identifying each metabolite that has a same level when compared with the [abnormal] level of that respective metabolite in the abnormal profile.

9. (Amended) The method of Claim 8 wherein the comparing the patient profile with respect to the abnormal profile step is accomplished by comparing the levels of metabolites in the patient profile with the mean levels and standard deviations for each respective metabolite of the abnormal profile.

10. (Amended) The method of Claim 8 wherein comparing the patient profile with respect to the abnormal profile step is accomplished by [comparing median levels using a nonparametric analysis for each metabolite.] using a nonparametric analysis to compare the levels of metabolites in the patient profile with the median levels of each respective metabolite of the abnormal profile.

11. (Amended) The method of Claim 8 [further comprising] wherein the analyzing step comprises:

determining if a formiminoglutamic acid level of the patient profile is less than a formiminoglutamic acid level of the abnormal profile,

determining if a homocysteine level of the patient profile is increased relative to a homocysteine level of the abnormal profile,

determining if a normetanephrine level of the patient profile is increased relative to a normetanephrine level of the abnormal profile,

determining if an oxalic acid level of the patient profile is decreased relative to an oxalic acid level of the abnormal profile,

determining if a serine level of the patient profile is decreased relative to a serine level of the abnormal profile, and

determining if a tetra-hydro-biopterin level of the patient profile is decreased relative to a tetra-hydro-biopterin level of the abnormal profile.

[inferring an activity level for an enzyme that corresponds to an identified metabolite having a same level as a metabolite in the abnormal profile, and]

[inferring a cofactor level based on the activity level for the enzyme.]